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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/484,340	06/07/95	SMITH L	243132000105

EXAMINER

HM21/0826

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ART UNIT	PAPER NUMBER
1634	26

DATE MAILED: 08/26/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/29/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 75-77, 81-83, 88, 98-103, 105-109, 109-138 is/are pending in the application.
Of the above, claim(s) 112-117 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 75-77, 81-83, 88, 98-103, 105-107, 109-111, 118-138 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☒ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

DETAILED ACTION

1. This action is in response to papers filed 01/23/98 in which claims 92-97 and 104 were canceled, claims 75-77 81-83, 88, 98-103, 105-107, 109-111, 118-132 were amended and claims 133-138 were added. Currently, claims 75-77, 81-83, 88, 98-103, 105-107, 109-138 are pending. Claims 112-117 are withdrawn from further consideration as being drawn to a non-elected invention. All of the amendments and arguments have been thoroughly reviewed. This action is made non-final because new grounds of rejection are added.

2. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

3. Any rejections not reiterated below are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow.

4. It is noted that claim 121 has been amended by the Examiner as follows (see interview summary dated July 08, 1998): "[primers" was deleted and --primers [-- was inserted.

Claim Rejections - 35 USC § 112

5. Claims 77, 83, 100, 103, 107, 120-123, 127-134, 136-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 77, 83, 120, 133, 136 are rejected as indefinite over the recitation "has been separated"for the following reasons. It is unclear as to whether the claims are drawn to an

oligonucleotide primer itself or a primer extended and/or hybridized to a template. The phrase "has been", in past tense, makes the claims indefinite because it is unclear as to exactly when the primer was base-paired or extended or separated.

b. Claims 100, 103, 107, 127-132, 136-138 are rejected as indefinite over the recitation "5' end or in the vicinity thereof" because the claims do not provide a definition of what is encompassed by the vicinity of the 5' end and therefore, the scope of the claims cannot be determined. Vicinity is a relative term that does not adequately describe the metes and bounds of the claim.

Response to Arguments

Applicant traversed this rejection. The response argues that vicinity is clearly defined by the specification at page 9 which states that the 5' end or vicinity thereof is meant to denote a location sufficiently distant from the 3' end that is will not prevent 3' end extension. These arguments have been thoroughly reviewed but are deemed non persuasive for the following reasons. Page 9 of the specification states that the fluorophore or chromophore must not interfere with hybridization or prevent 3' extension but does not say that the fluorophore must be at the 5' end nor describe what is a "sufficient distance from the 3' end" so as not to interfere. Therefore, for all of these reasons and those reasons already of record, the rejection is maintained.

c. Claims 120, 133, 136 are rejected as indefinite over the recitation of the phrase "duplex of claim 77" because claim 77 is an oligonucleotide and not a duplex and this phrase therefore lack proper antecedent basis.

d. Claims 121-123, 134, 137 are rejected as indefinite over the recitation of the phrase "the set of primers of claims 81 to 83" because claims are not drawn to a set of primers but a set of duplexes and set of oligonucleotides and therefore this phrase lacks proper antecedent basis.

Claim Rejections - 35 USC § 103

6. Claims 75-77, 81-83, 88, 98, 100-101, 103-105, 107, 109-111, 118-132, 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qu et al (Nucleic Acids Research (Sept. 1983) 11:5903-5920; hereinafter Qu) or in the alternative Hindley (Proc. FEBS Symp: DNA-Recombination Interactions and Repair (1980) Pergamon Press, New York, pp. 143-154; hereinafter Hindley) each in view of Langer *et al.* (*Proc. Natl. Acad. Sci., USA* (Nov. 1981) 78:6633-6637; hereinafter Langer) and each further in view of Leary *et al.* (*Proc. Natl. Acad. Sci., USA* (July 1983) 80:4045-4049; hereinafter Leary).

Qu teaches a method of extending a 5' end labelled DNA primer in the presence of a RNA template and a reverse transcriptase, e.g. a polymerase (abstract and paragraph bridging pages 5904-5905, page 5906 & Figures 1 & 2). Qu teaches compositions of 1) the primer and template, 2) extended primer/template hybrids and 3) the extended primer alone (page 5906, lines 11, 18-19, and 22, respectively). Qu teaches the use of a radioactive label and not a chromophore or fluorophore.

Hindley teaches a method of DNA sequencing using a 5' end labelled DNA primer in the presence of a template and a polymerase (abstract, paragraph bridging pages 146-147). Hindley

teaches compositions of 1) the primer and template, 2) extended primer/template hybrids and 3) the extended primer alone (paragraph bridging pages 146-147). Hindley teaches the use of a radioactive label and not a chromophore or fluorophore.

Langer teaches making biotinylated nucleotides. Langer teaches that such probes containing biotin groups provide a suitable alternative to radioisotopes for nucleic acid detection (page 6633, first paragraph). Langer teaches that avidin can be coupled to an appropriate indicator molecules such as a fluorescent dye which will then specifically detect the biotinylated oligonucleotide (page 6633, first paragraph). Langer teaches that the modified nucleotide are substrates for polymerases and that oligonucleotide containing the biotinylated nucleotide have properties similar to those of unmodified oligonucleotide, including specifically and efficiently hybridization to complementary sequences (abstract & page 6637 first paragraph).

Leary teaches method of making biotinylated probes for use in hybridization reactions using nick translation methods (page 4046, paragraph bridging col. 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the fluorophore/avidin/biotinylated oligonucleotide label of Langer & Leary for the radioactive label of Qu or Hindley to have improved the method of Qu or Hindley by having obviated the need for hazardous and expensive radiochemicals with a limited half-life. One of ordinary skill in the art at the time the invention was made would have been motivated to have used the methods of Langer & Leary to have provided a biotinylated oligonucleotide probe where the probe was made by nick translation in the presence of a limited

number of biotinylated nucleotide analogs to have made a labeled oligonucleotide that could have then been detected using a fluorescently labeled avidin molecule, according to the teachings of Langer. Because of the teachings of Langer that such modified oligonucleotides behave nearly identical to their unmodified counterparts, the ordinary artisan would have had a reasonable expectation of success that such biotinylated oligonucleotides could have been used in the method of Qu or Hindley and, as discussed above, would have improved the method of Qu or Hindley by having obviated the need for radioactivity. It is noted that the instantly claimed invention does not specify how the oligonucleotide are to be modified but that there is a chemical coupling between the label and the primer. The label of Langer & Leary which provides for nucleic acid detection using a fluorescent label/avidin/biotin system is chemically coupled to the oligonucleotide and therefore renders the instantly claimed invention obvious. In the case of the teachings of Langer & Leary, the biotin moiety covalently modifies the nucleotide incorporated into the primer and the avidin is covalently modified with a fluorescent molecule, the biotin and avidin are chemically coupled as the interaction between the biotin and avidin, involving VanDerWaals forces, hydrophobic interactions and hydrogen bonding is a chemical coupling. In light of the conventionality of kits in the nucleic acid arts at the time the invention was made, it would have further been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the polymerase and labeled primer of the teachings of Qu or Hindley in view of Langer & Leary into a kit, thereby providing a set of reagents, for the convenience of the practitioner wishing to practice nucleic acid sequencing as taught by Qu or

Hindley in view of Langer & Leary. It is noted that claims 98-103, 105-107, 127-132 are product by process claims and are not limited to products made by the claimed method. Thus, in the absence of evidence to contrary, the burden is upon the applicant to prove that the claimed oligonucleotides are different from those taught by the prior art and to establish patentable differences (See In re Best 562 F.2d 1252 195 USPQ 430 (CCPA) and Ex parte Gray 10 USPQ 2d 1922 (PT) Bd. Pat. Appeals & Int, 1989).

Response to Arguments

Applicant traversed this rejection. To the extent these arguments apply to the new grounds of rejection, these arguments have been thoroughly reviewed but are deemed non persuasive for the following reasons. The response argues that the art of Langer and Leary is not capable of generating tagged oligonucleotide according to the present invention because the biotinlyated probes of the prior art require interaction with labeled avidin for detection while the instant oligonucleotide are inherently detectable. These arguments have been thoroughly reviewed but are deemed non persuasive because what is claimed is a product, not a method of detecting or any other method. The product must be chemically coupled to a fluorophore or chromophore. As discussed above, the biotinylation/avidin/fluorophore system provides the instantly claimed composition. The response argues that the method of labeling as taught by Leary would not make the sequence defined oligonucleotide of the instant invention as nick translation insert an unpredictable number of labeled nucleotides at random positions. These arguments have been thoroughly reviewed but are deemed non persuasive because nick translation is a template driven

process and therefore inserts labeled nucleotide into a primer according to template sequence and does provide a labeled primer of defined sequence. The response argues that a double-stranded DNA is required for nick translation as taught by Leary and denaturation of the double stranded molecule so labeled would product a heterogeneous collection of fragments unsuitable for primer use. These arguments have been thoroughly reviewed but are deemed non persuasive because the claims are drawn to a composition that comprises at least one labeled primer and a template. It is not a claimed limitation that all the primers be of the same size or sequence. The response argues that the nick translation method of Leary risk interfering with the 3' extension end of the primers. These arguments have been thoroughly reviewed but are deemed non persuasive because the art of Langer demonstrates that the biotinylated primers are recognized and therefore can be used by polymerases which, as discussed above, provides the ordinary artisan with a reasonable expectation of success of using the labeling method of Langer & Leary in the method of Qu or Hindley.

7. Claims 75-77, 81-83, 88, 98-103, 105-107, 109-111, 118-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qu or in the alternative Hindley each in view of Smith et al (U.S. Patent 5,118,800, Jun 02, 1992;effective fling date Dec. 20, 1983; hereinafter Smith).

As discussed above, both Qu and Hindley teach a method of extending a 5' end labelled DNA primer in the presence of a template and a polymerase but do not teach the use of a chromophore or fluorophore as a label.

Smith teaches that there are many reasons to want to covalently attach chemical such as fluorescent dyes to oligonucleotide, for use for example for use in DNA sequencing, such as improving the shelf-life and availability of the labeled primer, eliminating radioisotope use and permitting the automation of the method (col. 3 lines 58-68). Specifically Smith teaches methods for generating an 5' amino terminal oligonucleotide and conjugation of a fluorescent dye to this amino terminus (schemes 11 and 12 in col. 31-32 & col. 35). It is noted that the Smith patent is awarded benefit of the filing date of the earliest priority document, Dec. 20, 1983, because the 06/565,010 document discloses labeling of oligonucleotides covalently with fluorophores as discussed above (in particular schemes 11 and 12 of Smith and the col. 3-4 of Smith are described). It is further noted that the inventive entity of the Smith patent and the instant Application are different so that the Smith patent qualifies are prior art under 35 USC 102(e).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the fluorophore labeled primers of Smith for the radioactively labeled primers of Qu or Hindley to have improved the method of Qu or Hindley by having obviated the need for hazardous and expensive radiochemicals with a limited half-life. Further, in light of the conventionality of kits in the nucleic acid arts at the time the invention was made, it would have further been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the polymerase and labeled primer of the teachings of Qu or Hindley in view of Smith into a kit, thereby providing a set of reagents, for the convenience of the practitioner wishing to practice nucleic acid sequencing as taught by Qu or Hindley in view

of Smith. It is noted that claims 98-103, 105-107, 127-132 are product by process claims and are not limited to products made by the claimed method. Thus, in the absence of evidence to contrary, the burden is upon the applicant to prove that the claimed oligonucleotides are different from those taught by the prior art and to establish patentable differences (See In re Best 562 F.2d 1252 195 USPQ 430 (CCPA) and Ex parte Gray 10 USPQ 2d 1922 (PT) Bd. Pat. Appeals & Int, 1989).

8. Claims 75-77, 81-83, 88, 98, 100-101, 103-105, 107, 109-111, 118-132, 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qu or in the alternative Hindley each in view of Levinson *et al* (*Biochim.Biophys. Acta* (Oct. 1976) 447:260-273; hereinafter Levinson).

As discussed above, both Qu and Hindley teach a method of extending a 5' end labelled DNA primer in the presence of a template and a polymerase but do not teach the use of a chromophore or fluorophore as a label.

Levinson teaches making fluorescently labeled DNA by reaction of the fluorophore acriflavin with aldehydes of depurinated DNA (abstract). Levinson teaches that this labeling procedure should be useful in place of radioactive labeling of DNA (abstract). Levinson teaches that the rate of depurination of the DNA is 0.7%purines/hr (page 264) and teaches only using partially depurinated DNA for acriflavin labeling (page 262).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted acriflavin labeled primers of Levinson for the radioactively

labeled primers of Qu or Hindley to have improved the method of Qu or Hindley by having obviated the need for using radioactivity. Further, in light of the conventionality of kits in the nucleic acid arts at the time the invention was made, it would have further been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the polymerase and labeled primer of the teachings of Qu or Hindley in view of Levinson into a kit, thereby providing a set of reagents, for the convenience of the practitioner wishing to practice nucleic acid sequencing as taught by Qu or Hindley in view of Levinson. It is noted that claims 98-103, 105-107, 127-132 are product by process claims and are not limited to products made by the claimed method. Thus, in the absence of evidence to contrary, the burden is upon the applicant to prove that the claimed oligonucleotides are different from those taught by the prior art and to establish patentable differences (See In re Best 562 F.2d 1252 195 USPQ 430 (CCPA) and Ex parte Gray 10 USPQ 2d 1922 (PT) Bd. Pat. Appeals & Int, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Debra Shoemaker whose telephone number is (703) 305-4048 and by fax (703) 305-8724 for informal or draft papers. The examiner can normally be reached on 7:30 AM-4:00 PM from Monday to Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242 for official faxes.

Any inquiry of an a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Debra Shoemaker
August 14, 1998

STEPHANIE W. ZITOMER
PRIMARY EXAMINER